

CLAIMS:

1. A composition containing the following active substances A and C, wherein:

A = at least one GLP-1/GLP-1-like peptide, preferably GLP-1(7-34)-amide and/or GLP-1(7-36)-amide;

C = at least one guanylate cyclase C activating peptide from the guanylin and/or uroguanylin genes, preferably guanylin-101-115 and/or uroguanylin-89-112.

2. The composition according to claim 1, characterized by additionally containing an active substance B which is a substance inhibiting the degradation of a cyclic nucleotide.
3. The composition according to claim 2, wherein the active substance B is a phosphodiesterase inhibitor, preferably a group III and/or IV phosphodiesterase inhibitor.
4. The composition according to any of claims 1 to 3 in combination with one or more peptide hormones which affect the islet cell secretion, such as the hormones of the secretin/gastric inhibitory peptide (GIP)/vasoactive intestinal peptide (VIP)/pituitary adenylate cyclase activating peptide (PACAP)/glucagon-like peptide II (GLP-II)/glicentin/glucagon gene family and/or those of the adrenomedullin/amylin/calcitonin gene related peptide (CGRP) gene family.
5. The composition according to at least one of claims 1 to 4, wherein the active substance A is GLP-1 and is used as GLP-1(7-34), GLP-1(7-

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35), GLP-1(7-36) or GLP-1(7-37) in its C-terminally carboxylated or amidated form.

6. The composition according to at least one of claims 1 to 5, wherein, in the active substance GLP-1, the amino acid lysine in position 26 and/or 34 is substituted by a neutral amino acid, arginine or a D-form of lysine or arginine; and/or arginine in position 36 is substituted by a neutral amino acid, arginine or a D-form of arginine or lysine.
7. The composition according to at least one of claims 1 to 6, wherein, in the active substance GLP-1, tryptophan in position 31 is substituted by an oxidation-resistant amino acid.
8. The composition according to at least one of claims 1 to 7, wherein, in the active substance GLP-1, at least one amino acid given for the respective position is respectively substituted by following amino acids:
  - Y for V in position 16;
  - K for S in position 18;
  - D for E in position 21;
  - S for G in position 22;
  - R for Q in position 23;
  - R for A in position 24; and
  - Q for K in position 26.
9. The composition according to at least one of claims 1 to 8, wherein, in GLP-1, at least one amino acid given for the respective position is respectively substituted by following amino acids:
  - a small neutral amino acid for A in position 8;
  - an acidic or neutral amino acid for E in position 9;

a neutral amino acid for G in position 10; and  
an acidic amino acid for D in position 15.

10. The composition according to at least one of claims 1 to 9, wherein, in the active substance GLP-1, the amino acid histidine in position 7 is substituted by a neutral amino acid or the D-form or N-acetylated or N-alkylated form of histidine wherein the amino acids for the stated substitutions are in either the D- or L-form, and the amino acid substituted in position 7 is in either its N-acetylated or its N-alkylated form.
11. The composition according to claims 1 to 10, wherein the amino acid lysine in positions 26 and/or 34 is substituted by K<sup>+</sup>, G, S, A, L, I, Q, M, R and R<sup>+</sup>, and the amino acid arginine in position 36 is substituted by K, K<sup>+</sup>, G, S, A, L, I, Q, M and R<sup>+</sup>.
12. The composition according to claims 1 to 11, wherein the amino acid tryptophan in position 31 is substituted by F, V, L, I, A and Y.
13. The composition according to claims 1 to 12, wherein the modification stated in claim 6 is combined with at least one of the substitutions S for G in position 22, R for Q and A in positions 23 and 24, and Q for K in position 26, or these substitutions are additionally combined with a substitution of D for E in position 21.
14. The composition according to claims 1 to 13, wherein alanine in position 8 is substituted by a small neutral amino acid from the group consisting of S, S<sup>+</sup>, G, C, C<sup>+</sup>, Sar, A<sup>+</sup>, beta-ala and Aib and wherein the acidic or neutral amino acid substituted for glutamic acid in position 9 is selected from the group consisting of E<sup>+</sup>, D, D<sup>+</sup>, Cay, T, T<sup>+</sup>, N, N<sup>+</sup>, Q, Q<sup>+</sup>, Cit, MSO and acetyl-K, and wherein the neutral amino acid substituted for glycine in position 10 is selected from the group

consisting of S, S<sup>+</sup>, Y, Y<sup>+</sup>, T, T<sup>+</sup>, N, N<sup>+</sup>, Q, Q<sup>+</sup>, Cit, MSO, acetyl-K, F and F<sup>+</sup>.

15. The composition according to claims 1 to 14, wherein the amino acid substituted for histidine in position 7 is selected from the group consisting of H<sup>+</sup>, Y, Y<sup>+</sup>, F, F<sup>+</sup>, R, R<sup>+</sup>, Orn, Orn<sup>+</sup>, M, M<sup>+</sup>, N-formyl-H, N-formyl-H<sup>+</sup>, N-acetyl-H, N-acetyl-H<sup>+</sup>, N-isopropyl-H, N-isopropyl-H<sup>+</sup>, N-acetyl-K, N-acetyl-K<sup>+</sup>, P and P<sup>+</sup>.

16. The composition according to claims 1 to 15, wherein the modified peptide is:

(H<sup>+</sup>)7-GLP-1(7-37);  
(Y)7-GLP-1(7-37);  
(N-acetyl-H)7-GLP-1(7-37);  
(N-isopropyl-H)7-GLP-1(7-37);  
(A<sup>+</sup>)8-GLP-1(7-37);  
(E<sup>+</sup>)9-GLP-1(7-37);  
(D)9-GLP-1(7-37);  
(D<sup>+</sup>)9-GLP-1(7-37);  
(F<sup>+</sup>)10-GLP-1(7-37);  
(S)22(R)23(R)24(Q)26-GLP-1(7-37); and/or  
(S)8(Q)9(Y)16(K)18(D)21-GLP-1(7-37).

17. The composition according to claims 1 to 16, wherein a peptide is used which has an increased resistance to degradation in the plasma as compared to GLP-1(7-34), GLP-1(7-35), GLP-1(7-36) or GLP-1(7-37) or the C-terminal amide, and/or has at least one of the following modifications:

(α) substitution of histidine in position 7 by the D-form of a neutral or acidic amino acid or the D-form of histidine;

( $\chi$ ) substitution of histidine in position 7 by an N-acylated (1-6C) or N-alkylated (1-6C) form of an alternative amino acid or histidine.

18. The composition according to claim 17, wherein histidine in position 7 is substituted by an amino acid from the group consisting of P<sup>+</sup>, D<sup>+</sup>, E<sup>+</sup>, N<sup>+</sup>, Q<sup>+</sup>, L<sup>+</sup>, V<sup>+</sup>, I<sup>+</sup> and H<sup>+</sup>.
19. The composition according to claim 17 or 18, wherein the D-amino acid in position 8 is substituted by an amino acid from the group consisting of P<sup>+</sup>, V<sup>+</sup>, L<sup>+</sup>, I<sup>+</sup> and A<sup>+</sup>.
20. The composition according to any of claims 17 to 19, wherein the D-amino acid in position 8 is substituted by an alkylated or acetylated amino acid from the group consisting of P, D, E, N, Q, V, L, I, K, and H.
21. The composition according to any of claims 17 to 20, wherein the modified peptide is:  
  
(H<sup>+</sup>)7-GLP-1(7-37);  
(N-acetyl-H)7-GLP-1(7-37);  
(N-isopropyl-H)7-GLP-1(7-37);  
(N-acetyl-K)7-GLP-1(7-37); and/or  
(A<sup>+</sup>)8-GLP-1(7-37).
22. The composition according to any of claims 1 to 21, wherein the active substances are present in a phosphorylated, acetylated and/or glycosylated form.

- papaverine;  
theophylline;  
enprofyllines; and/or  
IBMX.

25. The composition according to any of claims 2 to 24, wherein the phosphodiesterase inhibitors which inhibit group III phosphodiesterases (cGMP-inhibited phosphodiesterases) are:

adibendane (BM 14 478);  
milrinone (WIN 47203);  
enoximone (MDL 17043);  
pimobendane (UD-CG 115);  
MCI-154;  
saterinone (BDF 8634);  
sulmazole (ARL 115);  
UD-CG 212;  
motapizone;  
piroximone;  
ICI 118233

26. The composition according to any of claims 2 to 25, wherein the phosphodiesterase inhibitors which inhibit group IV phosphodiesterases (cAMP-specific phosphodiesterases) are:

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rolipram ZK 62711; pyrrolidone);  
imidazolidinone (RO 20-1724);  
etazolate (SQ 65442);  
denbufylline (BRL 30892);  
ICI63197;  
and/or RP73401.

27. The composition according to any of claims 2 to 26, wherein the phosphodiesterase inhibitors which inhibit both group III and group IV phosphodiesterases are:

tolafentrine;  
zardaverine;  
EMD54622; and/or  
Org30029.

28. A compound having the general formula:

$$R-NH-HAEGTFTSDVSSYLEGQAAKEFIAWLVK-CONH_2,$$

wherein R = H or an organic compound having from 1 to 10 carbon atoms.

29. The compound according to claim 28, wherein R is the residue of a carboxylic acid.

30. The compound according to claim 29, wherein R is formyl, acetyl, propionyl, isopropionyl, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl.

- tolafentrine;  
zardaverine;  
EMD54622; and/or  
Org30029.

- R-NH-~~HA~~EGTFTSDVSSYLEGQAAKEFIAWLVK-CONH<sub>2</sub>,

29. The compound according to claim 28, wherein R is the residue of a carboxylic acid.

30. The compound according to claim 29, wherein R is formyl, acetyl, propionyl, isopropionyl, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl.

31. A medicament containing an effective amount of the composition according to any of claims 1 to 27 or a compound according to any of claims 28 to 30 for the therapy of insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, MODY (maturity-onset diabetes in young people), for the treatment of secondary hyperglycemias in connection with pancreatic diseases (chronic pancreatitis, pancreatectomy, hemochromatosis) or endocrine diseases (acromegaly, Cushing's syndrome, pheochromocytoma or hyperthyreosis), for the treatment of drug-induced hyperglycemias (benzothiadiazine saluretics, diazoxide or glucocorticoids), for the therapy of pathologic glucose tolerance, for the therapy of hyperglycemias, for the therapy of dyslipoproteinemias, for the therapy of adiposity, for the therapy of hyperlipoproteinemias and/or hypotensions.
32. The medicament according to claim 31, characterized in that said medicament is in a release form by which release is achieved permanently or in a pulsatile way.
33. The medicament according to claim 32, characterized in that said medicament is suitable for subcutaneous, intravenous, peroral, intramuscular or transpulmonary administration.
34. Use of a composition containing at least two of the following active substances A, B, C, wherein:
- A = at least one hormone stimulating the production of cAMP;
- B = at least one substance inhibiting the degradation of a cyclic nucleotide;
- C = at least one hormone stimulating the production of cGMP;

for the preparation of a medicament for the treatment of adiposity.

add  
aa1

add  
aa2

add  
a1